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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,827	06/20/2001	Mark E. Salvati	LD0250(NP)	4381

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EXAMINER	
SMITH, CAROLYN L	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/885,827	SALVATI ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04132004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/13/04 has been entered. Amended claim 1 and cancelled claim 9 are acknowledged.

The information disclosure statement filed 4/13/04 fails to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP § 609, because reference AM, 4AE, 4AF, 4AG, 4AJ, 5AD, 5AE, 5AG, 5AH, and 5AI are in a foreign language without an English translation. They have been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609, ¶ C(1).

Claims 1 (amended) and 2-7 are herein under examination.

Claims Rejected Under 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain (AR-LBD), does not reasonably provide enablement for a method of inhibiting the growth of hormone-dependent tumor cells by administering a selective androgen receptor modulator that exhibits antagonist activity in a hormone-dependent tumor while exhibiting no activity or agonist activity against other non-tumor tissues containing the

androgen receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants state that one "drug design technique enabled in this invention is iterative drug design" (page 10, lines 34-35). Applicants further state that "[i]n iterative drug design, crystals of a series of protein/ligand complexes are obtained" followed by the determination of three-dimensional structures of each complex (page 11, lines 16-19). However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said methods. As the science of protein crystallization is well known to be a trial and error procedure with unpredictable results (Drenth, page 1, lines 13-20), one skilled in the art would require clear and precise guidance to make any particular crystal in order to obtain structural coordinates for a three-dimensional model. Accordingly, it would be very difficult for a skilled artisan to make crystal structures of other androgen receptor complexes beyond that mentioned in the instant case where specific coordinates are disclosed. Due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation. Again, due to the unpredictability in the art, a skilled artisan could not reasonably expect to make and use the structural coordinates from any androgen receptor complex based on generic guidelines of making crystals without undue experimentation.

Applicants submit that the subject matter of claim 1 is enabled by the sixty-seven particular compounds provided in the specification (page 34) and particular teachings (pages 44-46). This statement is found unpersuasive as the table starting in the specification on page 34 lists compounds but no factual measurements for these compounds regarding the claim limitations of antagonist versus "no activity" or agonist activity. On page 44 of the specification, last three lines, it appears that tumor assays are described but only EC_{50} regarding agonist characterization as in the claims. On page 45 only a few compounds have tumor activity measurements versus agonist EC_{50} measuring. Therefore, Applicants' submission that the sixty-seven compounds are all enabled for the claimed method appears to be an allegation without factual support. In addition, there does not appear to be any evidence in the specification that even a single compound has been demonstrated or even specifically suggested to exhibit the "no activity" limitation in instant claim 1.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence

to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al. (P/N 6,004,554), in view of Zhi et al. (P/N 6,358,947) and Li et al. (P/N 6,469,024).

Thorpe et al. describe treating tumors by using immunological reagents to target tumor-associated vascular endothelial cells in combination with direct targeting of tumor cells (col. 3, lines 45-52 and Table II on col. 25-26). Thorpe et al. describe therapeutic agents that have cytotoxic or anticellular effect by suppressing growth or division of cells (col. 3, lines 57-64). Thorpe et al. describe these methods and compositions as applicable to solid tumors, including carcinomas of the prostate (col. 4, lines 1-11 and Fig. 15A). Thorpe et al. describe a therapeutic method employing an antibody having high selectivity for tumor cells and little or no reactivity with the cell surface of normal endothelial cells (col. 5, lines 30-36). Thorpe et al. describe therapeutics showing no significant reactivity with normal tissues, including kidney, brain, liver, bone marrow, prostate, thyroid, muscle, skin, or other normal organ or tissue (col. 25-26, lines 64-67). Thorpe et al. describe and therefore suggest attaching other agents to target the toxin moiety to a tumor, such as hormones (col. 30, lines 34-43). Thorpe et al. do not specifically mention selective androgen receptor modulators.

Zhi et al. describe compounds that modulate a process mediated by androgen receptors (col. 19, lines 20-23), including male hormone response diseases (col. 19, lines 26-27). Zhi et al. describe a method of treating prostate adenocarcinomas, carcinomas, benign prostatic

hypertrophy of prostate, and other hormone-dependent tumors by administering a pharmaceutically effective amount of a compound (col. 20, lines 9-25).

Li et al. describe methods for treating osteoporosis by administering a therapeutically effect amount of a compound which stimulates an increase in muscle mass (col. 5, lines 13-21 and col. 208, lines 50-52). Li et al. describe a method for increasing growth hormone levels by administering a compound (col. 5, lines 7-12). Li et al. describe using the compounds in combination with a selective androgen receptor modulator to treat, stimulate, and increase muscle mass, as well as reducing cachexia due to cancer (col. 44, lines 47-61). Li et al. describe using the compounds in combination with anti-tumor agents (col. 49, lines 1-4). Li et al. describe treating Alzheimer's disease (col. 45, line 51), anorexia (col. 45, lines 38-39), and muscular atrophy due to physical inactivity and bed rest (col. 46, lines 24-26) by administering a therapeutically effective amount of a compound (col. 45, lines 3-8; col. 208, lines 32-35; and col. 209, lines 7-9).

Thorpe et al. state that significant advances in chemotherapy have been made for some tumors, while other types of tumors resist chemotherapeutic intervention (col. 1, lines 39-41). Thorpe et al. point out the key to developing successful antitumor agents is to design them to selectively kill tumor cells while exerting little effect against normal tissues (col. 1, lines 65-67 and col. 2, line 1). Thorpe et al. state this has been difficult because of the few qualitative differences between neoplastic and normal tissues (col. 2, lines 1-3). Thorpe et al. state much research has focused on identifying tumor-specific "marker antigens" (col. 2, lines 3-6). As Thorpe et al. state, modifications can be made without departing from the spirit and scope of their invention (col. 31, lines 48-53), a skilled artisan in the art would have reasonable

expectation of success to enhance the methods for inhibiting and treating prostate tumors, as stated by Thorpe et al., by administering various compounds related to prostate, as stated by Zhi et al. and Li et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the administration of selective androgen receptor modulators (as stated by Zhi et al. and Li et al.) in the methods of inhibiting and treating prostate tumor cells (as stated by Thorpe et al.) with a reasonable expectation of success. The motivation to do so is given by Thorpe et al. who teach developing successful antitumor agents via selective target agents (col. 1, lines 65-67), and the teaching of Zhi et al. and Li et al. relating to compounds that target androgen receptors.

Thus, Thorpe et al., in view of Zhi et al. and Li et al. motivate the instant invention.

Applicants state the combination of Thorpe et al., Zhi et al., and Li et al. references do not provide the feature of instant claim 1 regarding a SARM that (i) exhibits antagonist activity inhibiting growth of said hormone-dependent tumor and (ii) exhibits no activity or agonist activity against other, nontumor tissues containing the androgen receptor. This statement is found unpersuasive as various passages in the prior art references support this concept. For example, Li et al. describe using compounds in combination with a selective androgen receptor modulator (SARM) to treat, stimulate, and increase muscle mass (agonist activity of the combination including the SARM) and reduce cachexia due to cancer as well as using anti-tumor agents (antagonist activity of the combination including the SARM) (see details in 35 U.S.C.

rejection above). The "comprising" terminology recited in instant claim 1, line 2, is reasonably interpreted such that other compounds may be combined in the administering to a patient.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

June 10, 2004

Ardin H. Marschel 6/23/04
ARDIN H. MARSCHEL
PRIMARY EXAMINER